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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/465,925	12/17/99	ROSSI J	2124-314

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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No.	Applicant(s)	
	09/465,925	ROSSI ET AL.	
	Examiner	Art Unit	
	Andrew Wang	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☒ Other: *Notice to Comply* .

DETAILED ACTION

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 5,827,935. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed methods of colocalizing modified ribozymes would embrace the modified ribozymes as claimed in '935.

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-9 are rejected under 35 U.S.C. 102(a) as being anticipated by Sullenger *et al.* (Science).

The invention of the above claims is drawn to a method of localizing a ribozyme in a target cell wherein the ribozyme comprises a localization signal such as a dimerization signal.

Sullenger discloses a method wherein a ribozyme, tethered to a localization signal, B2A RNA, that forms a dimerization signal for viral particle colocalization. Furthermore, Sullenger discloses that the construct can be used for HIV.

Therefore, the invention of the above claims has been anticipated by Sullenger *et al.* (Science).

Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Sullenger *et al.* (Cell).

Sullenger discloses a $tRNA^{met}$ -TAR construct that was used to colocalize the target and inhibitor in HIV. Sullenger also discloses that a ribozyme or antisense oligo can be attached to the construct to inhibit HIV-1 replication.

Therefore, the invention of the above claims has been anticipated by Sullenger *et al.* (Cell).

Claims 1-9 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 5,854,038 ('038).

'038 discloses methods of colocalizing and inhibiting HIV-1 by administering a ribozyme construct comprising a viral dimerization domain.

Therefore, the invention of the above claims has been anticipated by US Patent No. 5,854,038.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for claims limited to a method of colocalizing an inhibitory agent comprising a localization signal in cells, *in vitro*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The invention of the above claims is broadly drawn to a method of colocalizing an inhibitory agent thus inhibiting a target molecule *in vivo* (whole animals) or *in vitro*. The specification provides guidance and examples demonstrating colocalization of a target molecule and a ribozyme in viruses wherein the ribozyme was attached to a $tRNA^{lys}$ molecule that formed a

dimerization domain with HIV-1, *in vitro*. The specification further shows the attachment of a U6 snRNA to a ribozyme which led to nuclear localization of a ribozyme, *in vitro*.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed constructs in *in vivo* methods of inhibition or in methods of treatment. Although the specification prophetically considers and discloses general methodologies of using the claimed constructs in methods of treatment, such a disclosure would not considered enabling since the state of the oligo and gene therapy is highly unpredictable.

The specification as filed does not enable the therapeutic use of antisense or ribozyme oligos since the clinical application of oligo therapy is a highly unpredictable art due to obstacles that still face oligo therapy as summarized by Agrawal who states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering in the disease process" (page 376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. [c]ellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum.[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the

oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379). Branch further elucidates the unpredictability of oligo therapy by stating that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (page 46, second column) and "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (page 45, third column). Additionally, in a recently published review of the potential use of antisense oligos as therapeutic agents, Gewirtz *et al.* teach that the inhibitory activity of an oligo depends unpredictably on both the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target (page 3161, second and third columns). Gewirtz *et al.* and Branch conclude by observing that, "the antisense approach has generated controversy with regard to mechanism of action, reliability, and ultimate therapeutic utility" and "that efforts should be increased...to learn how they may be used successfully in the clinic" (page 3162, middle column, last paragraph) and "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case-by-case basis." (page 50), respectively.

Thus, the specification fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges in the oligo therapy art that are exemplified in the

references above. Applicants should note that although the references particularly discuss antisense therapy, said references would still be applicable since antisense and ribozyme therapy require analogous methodologies.

Furthermore, the instant specification fails to provide one of skill in the art guidance for the selection of pharmaceutical oligo compounds without undue trial and error experimentation since it is clear from the references above that *in vitro* and cellular screening do not correlate with pharmaceutical oligo compounds that function in an *in vivo* environment. The specification in general fails to provide adequate guidance to overcome the obstacles and unpredictability of oligo therapy that are exemplified in the references above.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

It is noted that applicants have indicated that a computer diskette (CRF) containing the sequence listing was submitted but unfortunately said CRF could not be located. A new CRF with a declaration is required.

A full response to this Office action will require submission of the CRF.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew Wang whose telephone number is (703) 306-3217. The examiner can normally be reached on Monday to Thursday from 7:00 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Andrew Wang
January 5, 2001

Andrew Wang
Patent Examiner
Technology Center 1600

ANDREW WANG
PATENT EXAMINER